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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/945,459	12/09/97	MAKISHIMA	146.1275

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EXAMINER	
ROMEO,D	

ART UNIT	PAPER NUMBER
1647	20

DATE MAILED: 06/30/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/945,459	Makishima et al.
Examiner	**Group Art Unit**
David S. Romeo	1647

☒ Responsive to communication(s) filed on *19 Apr 2000* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-7 and 9-16* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-7 and 9-16* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. The Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1647.

2. The request filed on 04/19/00 (Paper No. 18) for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08945459 is acceptable and a CPA has been established. An action on the CPA follows.

3. Claims 1-7, 9-16 are pending and are being examined.

4. Any objection or rejection of record that is not maintained in this Office action is withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. Applicants' arguments have been fully considered but they are not persuasive. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account

only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper.

6. Claim 16 is rejected under 35 U.S.C. § 112, second paragraph, over the recitation of "a part is substituted" (lines 4-5) because it is unclear which "part" and how much of a "part" is substituted. The metes and bounds of the claim(s) are not clearly set forth.

7. Claim 16 is rejected under 35 U.S.C. § 112, second paragraph, over the recitation of "encoded amino acid sequence" (line 7). The antecedent basis of this limitation is unclear. A nucleotide sequence has six reading frames, three forward and three reverse, and encodes at least six different amino acid sequences. It is unclear which "encoded amino acid sequence is intended". It is suggested that the claim recite "without alteration of the amino acid sequence of said protein".

New formal matters, objections, and/or rejections:

8. ***Claim Objections***

Claim 9 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the

claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. It cannot be determined whether the transitional phrase "contains" are inclusive and open-ended or exclusive and closed. For the purpose of this objection the term has been interpreted as open. A claim which depends from a claim which "consists of" the recited elements or steps cannot add an element or step. Claim 9, which depends from claim 16 wherein the plasmid "consists of" the recited sequence, cannot add sequence to the plasmid. See MPEP 2111.03.

9. ***Claim Rejections - 35 USC § 101***

Claims 1, 2 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The invention as claimed reads on a product of nature. It is suggested that the claims be limited to an isolated polypeptide.

10. ***Claim Rejections - 35 USC § 112***

35 USC § 112, first paragraph

Claim 10 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are drawn to a recombinant method of making a polypeptide using a bacterial host

transformed with a plasmid comprising a DNA encoding the polypeptide wherein the polypeptide consist of the amino acid sequence of SEQ ID NO: 1. By necessity the synthesis of all proteins in all living organisms begins with methionine. SEQ ID NO: 1 does not begin with methionine. The specification lacks guidance for and lacks working examples of recombinantly making a protein that does not begin with a methionine. The instant specification has not told the skilled artisan how to accomplish such a feat. There is nothing in the prior art of record teaching how to accomplish such a feat. It would require undue experimentation for the skilled artisan to make and use the full scope of the claimed invention.

Claims 9, 16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claim 16 is directed to a process of making a protein with a plasmid capable of expressing a protein wherein the plasmid consist of the sequence of SEQ ID NO: 4. The specification has not told the skilled artisan how to make a plasmid capable of expressing a protein in a host cell wherein the plasmid consists of the sequence because of SEQ ID NO: 4 because promoters, ribosome binding sites, origins of replication, and so forth are necessary for the plasmid to be propagated in the host cell and express the protein encoded thereby. SEQ ID NO: 4 does not contain any of these elements necessary for the propagation of the plasmid and

expression of the encoded protein. It would require undue experimentation for the skilled artisan to make and use the full scope of the claimed invention.

35 USC § 112, second paragraph

The following claims are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 10 recites the limitations "monomer" and "monomer protein" in lines 9 and 10, respectively. There is insufficient antecedent basis for this limitation in the claim. It is suggested that the claims recite "protein" instead.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd.

App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 16 recites the broad recitation "a part is substituted", and the claim also recites "a plasmid ... which consists of DNA sequence of SEQ ID NO: 4" which is the narrower statement of the range/limitation.

Claim 16 is indefinite over the recitation of "consists of DNA sequence of SEQ ID NO: 4" because it is unclear if the plasmid consist of the sequence of SEQ ID NO: 4 or if the plasmid consist of some portion of the sequence of SEQ ID NO: 4. It is suggested that the claims recite "consists of the sequence of SEQ ID NO: 4".

11. ***Claim Rejections - 35 USC § 103***

Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Celeste (a10)[1] in view of Ben-Bassat (w10) and Hirel (u20).

Celeste teaches mature MP52 containing the amino acid sequence of SEQ ID NO:4 (column 3, lines 51-52). Amino acids #2 to #120 of Celeste's SEQ ID NO:4 are identical to applicants' SEQ ID NO:1. Celeste teaches that the first cysteine of the seven cysteine domain of MP52 is encoded by the codon beginning at nucleotide #899 of SEQ ID NO:3 (column 7, full

[1]References cited by the examiner are in an alphanumeric format, such as "a1", wherein the "a" refers to the reference cited on the Notice of References Cited, PTO-892, and the "1" refers to the Paper No. to which the Notice of References Cited, PTO-892, is attached.

paragraph 3). The codon beginning at nucleotide #899 of SEQ ID NO:3 encodes amino acid #19 of SEQ ID NO:4. Celeste teaches human MP52 proteins containing the amino acid sequence from amino acid #17 or #19 to #119 or #120 of SEQ ID NO:4 are expected to retain activity (column 7, full paragraph 3). Celeste teaches that the MP52 protein appears to begin at nucleotide 845 off SEQ ID NO:3 and continues through nucleotide 1204 of SEQ ID NO:3 (column 7, full paragraph 2). Celeste teaches that purified MP52 proteins may be produced by culturing a host cell transformed with a DNA sequence of SEQ ID NO:3 from nucleotide 845 to 1204 (column 7, full paragraph 3). Bacterial cells may also be suitable hosts (paragraph bridging columns 8-9) and the bacterially expressed MP52 can be isolated using techniques that are well known in the art (column 9, full paragraph 1). In expressing mature MP52 in a bacterial host, according to the teachings of Celeste, one would use a DNA molecule encoding a protein with the N-terminal sequence Met-Ala-Pro-. Celeste is silent with respect to a protein consisting of the amino acid sequence of SEQ ID NO: 1.

Ben-Bassat teaches that in the case of Met-Ala-Pro-IL2, 60% of the bacterially expressed protein also lost the alanine residue, while no alanine removal was detected from the in vitro methionine aminopeptidase (MAP) reaction. Ben-Bassat suggest that another aminopeptidase(s) might be responsible for the removal of the alanine residue. See page 735, paragraph bridging columns 1-2. Ben-Bassat also suggest obtaining a homogeneous protein product without the N-

terminal methionine; purified MAP could be used to "polish" the frayed amino terminal sequences (page 756, paragraph bridging columns 1-2).

Hirel teaches that the catalytic efficiency of MAP is insensitive to a Met-Pro- sequence, but that a variant with a Met-Ala-Pro- N-terminal sequence confirmed the inhibitory role of proline at position 3 (page 8250, column 2, full paragraph 4).

Ben-Bassat and Hirel do not teach a protein consisting of the amino acid sequence of SEQ ID NO: 1. However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to express mature MP52 in bacteria and to isolate the bacterially expressed protein therefrom, as taught by Celeste, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to express mature MP52 in bacteria because gene cloning and expression in bacteria would provide an abundant source of readily purified protein. In expressing mature MP52 in bacteria one of ordinary skill in the art would reasonably expect to obtain mature MP52 with the following N-terminal amino acid sequences, according to the teachings of Ben-Bassat and Hirel: Met-Ala-Pro, Ala-Pro, and Pro. The mature MP52 with a Pro at the N-terminus is identical to the claimed protein. The invention is prima facie obvious over the prior art.

Claims 1, 2 are rejected under 35 U.S.C. 103(a) as being unpatentable over Celeste (a10) in view of Ben-Bassat (w10) and Hirel (u20) as applied to claim 1 above and further in view of

Hotten (2, cited by Applicants) and Cerletti (n10). Celeste in view of Ben-Bassat and Hirel teach a protein consisting of the amino acid sequence of SEQ ID NO: 1. Celeste in view of Ben-Bassat and Hirel do not teach said protein where said protein is a homodimer. Hotten teaches that native GDF-5 is a dimer of the disulfide linked mature part of the protein as is seen in other TGF-β family members (page 650, first paragraph of discussion). GDF-5 is MP52. Cerletti teaches a process for the production of biologically active, dimeric, mature TGF-β-like proteins. The process comprises culturing an *E. coli* host that has been transformed with a plasmid containing DNA encoding the amino acid sequence of a mature TGF-β-like protein (page 7, lines 9-14 and lines 40-41), solubilizing inclusion bodies obtained by culturing said *E. coli*, purifying the monomer protein from the solubilized solution, refolding the monomer protein into a dimer protein, and purifying same (page 7, line 56 through page 8, line 15). Hotten and Cerletti do not teach a protein consisting of the amino acid sequence of SEQ ID NO: 1. However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to make a protein consisting of the amino acid sequence of SEQ ID NO: 1, as taught by Celeste in view of Ben-Bassat and Hirel, and to modify that teaching by forming native biologically active dimers, as taught by Hotten and Cerletti, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to combine these teachings in order to form the native, biologically active form of the protein. The invention is prima facie obvious over the prior art.

Claims 1-7, 11-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Celeste (a10) in view of Ben-Bassat (w10) and Hirel (u20) and further in view of Hotten (2, cited by Applicants) and Cerletti (n10) as applied to claims 1, 2 above and further in view of Neidhardt (1, cited by Applicants), Adams (c10), and Ethridge (d10).

Celeste in view of Ben-Bassat and Hirel and further in view of Hotten and Cerletti teach a mature, native, biologically protein consisting of the amino acid sequence of SEQ ID NO:1, wherein said protein is a homodimer, as discussed above.

Celeste in view of Ben-Bassat and Hirel and further in view of Hotten and Cerletti do not teach a pharmaceutical composition comprising a protein consisting of the amino acid sequence of SEQ ID NO:1, wherein said protein is a homodimer, and a pharmaceutically acceptable carrier. Celeste in view of Ben-Bassat and Hirel and further in view of Hotten and Cerletti do not teach administering such a pharmaceutical composition to a human in an amount effective to treat the recited cartilage or bone diseases.

Neidhardt teaches a pharmaceutical composition comprising MP52 and a pharmaceutically acceptable carrier for use in the healing of bone, cartilage, or tooth defects and discloses the administration of such a composition to humans (page 9, full paragraph 1).

Adams teaches inducing bone formation for the treatment of bone fracture, osteoporosis, and osteoarthritis (column 5, full paragraph 4).

Ethridge teaches inducing bone formation for the treatment of alveolar defects (column 7, full paragraph 2; claim 28).

Neidhardt, Adams, and Ethridge do not teach a pharmaceutical composition comprising a protein consisting of the amino acid sequence of SEQ ID NO:1, wherein said protein is a homodimer, and a pharmaceutically acceptable carrier. Neidhardt, Adams, and Ethridge do not teach do not teach administering such a pharmaceutical composition to a human in an amount effective to treat the recited cartilage or bone diseases.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to make a protein consisting of the amino acid sequence of SEQ ID NO:1, wherein said protein is a homodimer, as taught by Celeste in view of Ben-Bassat and Hirel and further in view of Hotten and Cerletti, and to modify that teaching by making a pharmaceutical composition comprising the homodimer and a pharmaceutically acceptable carrier, and to administer such a pharmaceutical composition to a human in an amount effective to treat bone, cartilage, or tooth defects, as taught by Neidhardt, Adams, and Ethridge with a reasonable expectation of success. One of ordinary skill in the art would be motivated to combine these teachings because Neidhardt, Adams, and Ethridge teach that such a composition would useful for such purposes. The invention is prima facie obvious over the prior art.

Conclusion

12. No claims are allowable.

13. SEQ ID NO: 4 is free of the prior art of record because Celeste (a10), Hotten (2, cited by Applicants), and Neidhardt (1, cited by Applicants) teach a "G" instead of an "A" at nucleotide 264 of SEQ ID NO: 4.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David S. Romeo whose telephone number is (703) 305-4050. The examiner can normally be reached on Monday through Friday from 6:45 a.m. to 3:15 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242.

Faxed draft or informal communications should be directed to the examiner at (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

David Romeo
DAVID ROMEO
PATENT EXAMINER
June 29, 2000